## REMARKS

1. Applicants hereby submit the following:

[ ] a paper copy of a "Sequence Listing", complying with §1.821(c), to be incorporated into the specification as directed above;

[XX] an amendment to the paper copy of the "Sequence Listing" submitted on January 2, 2001, the amendment being in the form of substitute sheets. Applicants deleted from the previously submitted sequence listing all sequences which contain D-amino acids (i.e., SEQ ID NOs:1-13 and SEQ ID NOs:16-28), in accordance with 37 C.F.R. §1.821(a)(2). Previously submitted SEQ ID NOs:14-15 are now SEQ ID NOs:1-2, and SEQ ID NOs:3-7 as submitted in the attached substitute sequence listing are the sequences as shown in Figure 9 all of which had erroneously been omitted from the previously submitted sequence listing.

[XX] the Sequence Listing in computer readable form, complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted,

all previously submitted data with the amendment incorporated therein;

[ ] pursuant to §1.821(e), reference is made to the computer readable form filed on , in USSN , which presents the identical Sequence information, the use of which is now requested, in lieu of submitting a new computer readable form; and/or

[ ] a substitute computer readable form to replace one found to be damaged or unreadable.

[XX] 2. The description has been amended to comply with §1.821(d).

3. The undersigned attorney or agent hereby states as follows:

(a) this submission is not believed to include new matter [§1.821(g)];

(b) the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are believed to be the same [§1.821(f) and §1.825(b)];

(c) if the paper copy has been amended, the amendment is believed to be supported by the

specification and is not believed to include new matter [§1.825(a)]; and

(d) if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is believed to be identical to that originally filed [§1.825(d)].

4. Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not

be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the specification:**

The paragraph beginning at line 27 of page 1 has been amended as follows:

Thus, Goodson et al. disclosed nineteen linear 15-mers comprising of two relatively short conserved subsequences: LWXXAr (Ar = Y, W, F or H) and XFXXYLW, neither of which are found in uPA or its receptor (uPAR). The peptides were tested in a uPAR binding assay, wherein the most potent inhibitor (the so-called "Clone 20": AEPMPHSLNFSQYLWYT (SEQ ID NO:2)) showed an apparent inhibition constant at 10 nM for the uPAR-ATF interaction.

The paragraph beginning at line 5 of page 33 has been amended as follows:

The "monomer" AE78 (i.e. the so-called "Clone 20" having the sequence: AEPMPHSLNFSQYLWYT (SEQ ID NO: 2)), on the other, lost the majority of its inhibitory activity after incubation with 10% mouse serum for 24 hours even though the concentration was 1000 fold (3 orders of magnitude) higher than that of AE118.

The paragraph beginning at line 7 of page 35 has been amended as follows:

*Fig. 9: Sequence comparison of the relevant amino acids subjected to alanine mutagenesis in human (SEQ ID NO:3) uPAR to the corresponding residues of hamster (SEQ ID NO:4), mouse (SEQ ID NO:5), rat (SEQ ID NO:6), and bovine (SEQ ID NO:7) uPAR.*

The paragraph beginning at line 7 of page 36 has been amended as follows:

The following peptides were synthesised using standard methodologies:

| | |
|---|---|
| *dChaFsrYLWS* | *(Code: dCha)* |
| *eChaFsyYLWS* | *(Code: AE100)* |
| *tChaFsrYLWS* | *(Code: AE108)* |
| *DchaFsrYLWS* | *(Code: AE105)* |
| *DChaFsrGYLWS* | *(Code: AE116)* |
| *DChaFsrβAYLWS* | *(Code: AE117)* |
| *DChaFSrYLWS* | *(Code: AE106)* |
| *dChaFSrYLWS* | *(Code: AE107)* |
| *SLChaFsQYLWS* | *(Code: Lcha)* |
| *dChaFsrYL$^2$nAS* | *(Code: AE109)* |
| *DChaFsRYLWS* | *(Code: AE110)* |
| *DchaFsrYL$^1$nAS* | *(Code: AE114)* |
| *eChaFsYYLWS* | *(Code: AE115)* |
| *SLNFSQYLWS* | *(Code: AE68) (SEQ ID NO:1)* |

| | |
|---|---|
| *AEPMPHSLNFSQYLWYT* | *(Code: AE78)* *(SEQ ID NO:2)* |
| *arFhhYLWS* | *(Code: AE104)* |
| *LNFsQYLWS* | *(Code: AE111)* |
| *DFFsrYLWS* | *(Code: AE112)* |
| *DNFsrYLWS* | *(Code: AE113)* |

The three paragraphs beginning at line 30 of page 38 and ending at line 15 of page 39 have been amended as follows:

The starting peptide sequence used was the peptide disclosed earlier by Chiron as Clone 20 (R.J. Goodson et al. (1994) *Proc. Nat. Acad. Sci. U.S.A.* 91:7129-7133). The peptide consists entirely of naturally occurring amino acids:

A E P M P H S L N F S Q Y L W Y T (AE78) (SEQ ID NO:2)

a) The effect of truncation of this peptide was first studied. Truncation was performed by (step-wise) elimination of sets of two amino acids from the C-terminal end and from the N-terminal end. By this procedure a 10-mer peptide was identified as the minimum sequence retaining good activity:

S L N F S Q Y L W S (AE68) (SEQ ID NO:1)

b) An alanine scan of this 10-mer was then performed in order to identify the functionally most important residues. The result obtained was:

S L N F S Q Y L W S (SEQ ID NO:1)

Table 2 on pages 51-52 has been amended as follows:

TABLE 2

Summary of off-rates determined by Biacore technology for various peptides selected by combinatorial chemistry

| Code | Sequence | SEQ ID NO | $k_{diss}$ ($sec^{-1}$) | Relative $k_{diss}$ [1)] |
|---|---|---|---|---|
| AE68[2)] | SLNFSQYLWS | 1 | $12.9 \times 10^{-3}$ | 92.1 |
| dCha | d-Cha-F-s-r-Y-L-W-S | | $0.68 \times 10^{-3}$ | 4.9 |
| AE100 | e-Cha-F-s-y-Y-L-W-S | | $0.56 \times 10^{-3}$ | 4.0 |
| AE108 | t-Cha-F-s-r-Y-L-W-S | | $0.48 \times 10^{-3}$ | 3.4 |
| AE105 | D-cha-F-s-r-Y-L-W-S | | $0.21 \times 10^{-3}$ | 1.5 |
| AE116 | D-cha-F-s-r-G-Y-L-W-S | | no binding | >>100 |
| AE117 | D-cha-F-s-r-ßA-Y-L-W-S | | no binding | >>100 |
| AE106 | D-Cha-F-S-r-Y-L-W-S | | $2.63 \times 10^{-3}$ | 18.7 |
| AE107 | d-Cha-F-S-r-Y-L-W-S | | $8.84 \times 10^{-3}$ | 63.1 |
| Lcha | S-L-Cha-F-s-Q-Y-L-W-S | | $3.49 \times 10^{-3}$ | 24.9 |
| AE109 | d-Cha-F-s-r-Y-$L^{2}$-nA-S | | $2.05 \times 10^{-3}$ | 14.6 |
| AE110 | D-Cha-F-s-R-Y-L-W-S | | $0.28 \times 10^{-3}$ | 2.0 |
| AE114 | D-Cha-F-s-r-Y-$L^{1}$-nA-S | | $0.59 \times 10^{-3}$ | 4.2 |
| AE115 | e-Cha-F-s-Y-Y-L-W-S | | $1.67 \times 10^{-3}$ | 11.9 |
| AE118 | $[DChaFsrYLWSG]_2$-K | | $0.04 \times 10^{-3}$ | 0.28 |
| AE120 | α-[DChaFsrYLWSGβA]-ε-[DChaFsrYLWSG]-K | | $0.03 \times 10^{-3}$ | 0.21 |
| AE130 | D-Cha-F-s-r-L-L-W-h | | $0.51 \times 10^{-3}$ | 3.6 |
| AE132 | D-Cha-F-s-r-Cha-L-W-l | | $0.53 \times 10^{-3}$ | 3.8 |
| AE131 | D-Cha-F-s-r-Y-L-Nal-h | | $0.56 \times 10^{-3}$ | 4.0 |
| AE78[3)] | AEPMPHSLNFSQYLWYT | 2 | $10.1 \times 10^{-3}$ | 72.1 |
| AE104 | a-r-F-h-h-Y-L-W-S | | no binding | >>100 |
| AE111[4)] | L-N-F-s-Q-Y-L-W-S | | $1.05 \times 10^{-3}$ | 7.5 |
| AE112 | D-F-F-s-r-Y-L-W-S | | $1.81 \times 10^{-3}$ | 12.9 |
| AE113 | D-N-F-s-r-Y-L-W-S | | no binding | >>100 |
| AE124 | D-Cha-F-s-r-DMB-f-TRA-MEA [5)] | | $5.61 \times 10^{-3}$ | 40.0 |
| AE125 | D-Cha-F-s-r-DMB-f-Bzl-MEA | | $0.74 \times 10^{-3}$ | 5.3 |
| AE126 | D-Cha-F-s-r-DMB-f-AMN-MEA | | $0.37 \times 10^{-3}$ | 2.6 |
| AE128 | D-Cha-F-s-r-MEA-DMB-f-AMN | | no binding | >>100 |

| Code | Sequence | SEQ ID NO | $k_{diss}$ ($sec^{-1}$) | Relative $k_{diss}$ 1) |
|---|---|---|---|---|
| AE129 | D-Cha-F-s-r-DMB-f-DMB-l | | $0.54 \times 10^{-3}$ | 3.9 |
| pro-uPA | | | $0.10 \times 10^{-3}$ | 0.72 |
| ATF | | | $0.12 \times 10^{-3}$ | 0.86 |
| GFD | | | $0.14 \times 10^{-3}$ | 1.0 |

Table 3 on page 52 has been amended as follows:

TABLE 3

Effect of various peptide antagonists in the inhibition of the binding of ATF to mono-layer cultures of human MDA-MB-231 breast cancer cells.

| Code | Sequence | SEQ ID NO | $IC_{50}$ (nM) |
|---|---|---|---|
| AE118 | $[DChaFsrYLWSG]_2$-K | | 2 |
| AE78 | AEPMPHSLNFSQYLWYT | 1 | 200 |
| AE105 | DchaFsrYLWS | | 10 |
| DFP-uPA | | | 1 |